REMARKS

Claims 9-15 and 17-25 are pending. Claims 9, 14, 17 and 20 have been amended. Claims 9 and 14 have been amended to clarify that Applicants are claiming a solid composition for oral administration to humans. Claims 17-24 were previously withdrawn by the Examiner. However, claims 17 and 20 are dependent on claim 9 and have been amended to conform to the amendments to that claim. The amendments are supported throughout the specification, particularly at paragraphs 0027, 0028 and 0030, which disclose and discuss solid compositions for oral administration. No new matter has been added. Applicants request rejoinder of dependent method claims 17 -24 upon allowance of the product claims.

Rejections Under 35 USC §103 Over Santini in View of Miura

Applicants are grateful for the withdrawal of the rejection of Claims 9-15 and 25 under 35 U.S.C. 103(a) as being unpatentable over Santini et al in view of Miura et al. (US 5,116,828, "Miura").

Rejections Under 35 USC §102

Claims 9-10 and 12 were rejected for alleged anticipation by Chopra et al, Demonstration of Thyromimetic Effects of 3,5,3'-Triidothyronine Sulfate (T3S) in Euthyroid Rats," Thyroid, 1996, 6(3): 229-232 ("Chopra"). The Examiner found that Chopra discloses a liquid composition of T3S (necessarily comprising a solvent or carrier) at does of 3.5 µg, 10.5 µg and 31.5 µg, which is administered by injection. The Examiner found that this disclosure would necessarily be able to carry out the "preamble limitation" of being an oral composition.

Applicants respectfully traverse. Claims 9-10 and 12 require a solid composition comprising T3S for oral administration. As the Examiner admits, Chopra discloses a liquid composition for i.p. injection; thus it cannot anticipate the claims. Applicants request withdrawal of this rejection.

Rejections Under 35 USC §103 Over Chopra in View of Miura or Miura and Chiang

Claims 11 and 13 were rejected for obviousness over Chopra in view of Miura. The Examiner found that in addition to disclosing a liquid composition, Chopra teaches that T3S exhibits thyromimetic effects and is approximately one fifth as active as T3, that adult and fetal tissues contain sulfatases that can convert T3S to T3 and that T3S exhibits the same potency as T4. The Examiner concluded that Chopra differs from the instant claims in that the disclosed compositions do not include T4, but that inclusion of T4 was obvious in light of Miura and the dosages of T3 and T4 disclosed therein. Claims 14-15 and 25 were rejected for alleged obviousness over Chopra in view of Miura in further view of Chiang US 2001/0051657 ("Chiang"). The Examiner concedes that Chopra and Miura fail to disclose a kit, but asserts that a kit would have been obvious in view of Chaing's disclosure of kits for treating conditions including hypothyroidism comprising 2 compositions.

Applicants respectfully traverse. In order to establish obviousness, it is necessary, *inter alia*, to (i) determine the scope of the prior art and (ii) the differences between the claimed subject matter and that of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Applicants point out that in order to establish a *prima facie* case of obviousness, the examiner must provide a showing that, *inter alia*, the cited prior art references teach or suggest all of the claim limitations and there is some suggestion or motivation to combine the references. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); MPEP §§2142 and 2143. Furthermore, a *prima facie* finding of obviousness cannot be established when the "improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct 1727, 1739 (2007). Lastly, a prima facie case of obviousness based on structural similarity is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. (MPEP 2144.09). Applicants submit that the cited references, whether taken alone or in combination, fail to teach or suggest the claimed solid compositions

for oral administration. Additionally, Applicants submit that the previously submitted data provides ample evidence of the unexpected advantages of the claimed compositions.

The Cited References Do Not Teach or Suggest the Claimed Solid Compositions for Oral Administration

As an initial matter, as pointed out supra, Chopra discloses a liquid composition comprising T3S for i.p, administration and neither teaches nor suggests a solid composition of T3S for oral use. The solid composition of claim 9 is not obvious because T3S is not itself a drug, but rather a prodrug which has to be converted into its active form: T3 (triiodothyronine). In this regard, the Examiner points out that Chopra teaches that endogenous sulfatases convert T3S to T3. More specifically, Chopra suggests that the conversion of T3S to T3 is carried out, to an important extent, by peripheral tissue sulfatases, contrary to previous observations attributing the conversion to intestinal microflora sulfatases (Chopra p. 231, left mid col.: "This rapid generation of T3 from T3S…. ."). Moreover, Chopra discloses that, even by i.v. or i.p. administration, the thyromimetic effect linked to the T3S conversion into T3 is rather inefficient, as the potency of T3S administered i.p. is only about 1/5 that of T3, thus confirming the previous findings of Santini.

It is well known that both i.p. and i.v. administration drive a drug (or a prodrug such as T3S) directly into the bloodstream, and from the bloodstream to peripheral tissues and organs. Therefore the i.p. and i.v. routes are considered those more directly and thus more efficiently conveying an active principle to peripheral tissues. See, e.g. Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition , McGraw-Hill Health Professions Division, 1996, Section I, p. 4-5 at p. 5, attached as Exhibit 1. This basic manual further states that oral administration is less predictable, in terms of drug availability , than parenteral administration. This confirms that the skilled artisan could not expect oral administration to have the same efficiency as observed by the i.p. route, thus pointing to the non-obviousness of the claimed solid, oral composition of T3S.

In the case of T3S, Chopra teaches that mainly in peripheral tissues, tissue sulfatases convert the prodrug T3S to the active drug, T3, but that this conversion has an overall low efficiency being sufficient to achieve a systemic effect of only about 1/5 of the potency achieved with T3 (as measured by serum levels). Given this inefficient conversion and activity of T3S Chopra observed by i.p. injection administration, the skilled artisan would not have been motivated to prepare or expect success from formulating T3S in a solid composition for oral administration. Indeed, the skilled artisan would have expected that oral administration would have resulted in an additionally limiting factor (a low drug permeation rate through the gastrointestinal tract to the peripheral tissues for the enzymatic conversion to T3), further delaying ,lowering or even potentially interfering with an already inefficient T3S to T3 conversion process. Thus, Chopra neither teaches nor suggests the claimed solid T3S compositions of claims 9-10 and 12. Additionally, as the Examiner concedes, Chopra neither teaches nor suggests the claimed solid, oral composition comprising a combination of T3S and thyroxine, T4; thus it cannot render obvious the compositions of claims 11, 13-15 and 25.

The secondary references fail to remedy these deficiencies. Miura teaches administration of T3 and T4 and neither teaches nor suggests the administration of T3S, let alone its administration in combination with T4. Similarly, Chiang, which was cited simply for its disclosure of kits, neither teaches nor suggests the claimed solid compositions of T3S alone or in combination with T4. Moreover, Miura, contrary to the present invention, is directed to administration of the active forms of the thyroid hormones (T4 and T3) which do not need to be converted by endogenous enzymes to be active. Thus, it provides no motivation to administer T3S alone or in combination with T4 and provides no expectation of success in administering the claimed solid, oral composition of T3S alone or in combination with T4.

Applicants submit that the combined cited references fail to teach or suggest the claimed solid compositions for oral administration and thus a prima facie case of obviousness has not been established.

The Claimed Oral Compositions Have Unexpected Advantages Over the Cited References

Applicants submit that the instant claims are not obvious over the cited references for the additional reason that the claimed invention has unexpected advantages over the prior art. As an initial matter oral compositions are significantly easier to administer and more convenient than compositions like those of Chopra requiring injection i.p. Moreover, as explained above, the skilled artisan would not have expected that the less efficient oral administration of a pro-drug like T3S, which Chopra established is inefficiently converted to the active T3, would result in clinical efficacy. Indeed, as thoroughly argued by the Applicant in the replies to the previous Office Actions, one skilled in the art would not have expected a therapeutic effect upon oral administration of T3S because (briefly summarizing the already submitted main points):

1) Oral administration is less predictable and results in less rapid availability than parenteral administration (see Goodman & Gilman): this means that the same composition, once administered orally, can't be expected to provide the same results as observed by a different administration route (in this case by i.p.);
2) T3S is a highly polar molecule (due to the sulfate group covalently linked to triiodothyronine) and since very low oral adsorption rates are usually expected for polar molecules, T3S would have not been expected to efficiently cross the GI system; and
3) Lopresti taught that T3S is an inactive metabolite with "no detectable biological activity" that is "poor(ly) absorb(ed)ption from the gastrointestinal tract".

In sum, Applicants submit that the skilled artisan would have no expectation that a solid composition of T3S could be administered orally and provide a therapeutic effect.

Nonetheless as established in the Declaration of Dr. Aldo Pinchera ("Pinchera Declaration") submitted with Applicants April 9, 2010 Amendment After Final and Response, the oral compositions of the invention were absorbed by the gastrointestinal system and metabolized to the active T_3 when administered to human subjects at doses of 20-160 μg of T_3S. This data is unexpected in view of the

inefficient conversion of T3S to T3 observed in Chopra using the more efficient i.p. administration. It also unexpected in view of the polar nature of T3S and both the teaching of Lopresti, that oral radio-labelled T_3S was inactive and presumably not absorbed by the GI tract, and in view of the large dosages of T_3S (e.g. 2930 μg) Santini discloses for **i.p.** administration.

Specifically, as Dr Pinchera explains 28 human subjects with surgically excised thyroids were administered a single dose of an oral composition of the invention containing 20, 40, 80 or 160 μg of T_3S. The gastrointestinal absorption of T_3S was assessed by serum levels of thyroid hormone including T_3S and triiodothyronine ("T_3") as both free T_3 ("FT_3") and total T_3 ("TT_3"). Subjects without thyroid glands have no endogenous thyroid hormone production; thus any measured thyroid hormone was due to the administered oral compositions. Pinchera Declaration, ¶ 5.

As shown in Figure 1 of the Pinchera Declaration, all subjects, regardless of dose, exhibited gastrointestinal absorption of the oral composition as shown by detection of T_3S in serum with a peak level two hours after administration of the oral composition. Pinchera Declaration, ¶ 6, 24.

In patients lacking a thyroid there is no endogenous T_3. Thus, all T_3 present in the subjects was the result of conversion of T_3S from the oral compositions to T_3 in vivo. By monitoring serum T_3S and TT_3 levels after administration of the oral T_3S compositions, it was determined that T_3S serum level are maintained for at least 48 hrs (Fig 1 and 2) and that it was converted to the clinically active TT_3 in a dose related fashion. Pinchera Declaration, ¶ 7, 25; Figure 2.

These results were unexpected given the inefficient conversion of T3S to T3 observed by Chopra after the more efficient i.p administration. They were also unexpected in view of the polar nature of T3S and the teaching of Lopresti that radio-labelled T_3S was not clinically active upon oral administration, Pinchera Declaration, ¶ 8, 26, and given the high dosages of **i.p.** T_3S taught by Santini.

In sum, Applicants submit that the instant claims are not obvious over the cited references for the additional reason that the claimed oral compositions have advantages which were unexpected in light of the teachings of the art.

CONCLUSION

In view of the preceding remarks, it is believed that claims 9-15 and 25 are in condition for allowance. Applicants request rejoinder of claims 17-24.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be due with the filing of this Amendment other than the fee for the three month extension of time. However, if any additional fees are deemed necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

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/M. Caragh Noone, Reg. No. 37,197/

M. Caragh Noone, Reg. No. 37,197
Bracco Research USA Inc.
305 College Road East
Princeton, NJ 08540
Tel: (609) 514-2454
Fax: (609) 514-2446